Journal of Surgical Oncology 62:40–45 (1996)

Is There a Role for Second-Look Laparotomy in the Management of Malignant Germ Cell Tumors of the Ovary? Experience at Institut Gustave Roussy

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The last two decades have seen great improvements in the management of patients with germ-cell tumors of the ovary. The initial treatment approach includes conservative surgery and cisplatin-based chemotherapy in most cases. At completion of chemotherapy, the role of second-look surgery remains questionable. We retrospectively analyzed the long-term outcome (median follow-up, 8 years) of 40 patients who received various chemotherapy regimens after primary surgery and focused on the role of second-look surgery. A second-look laparotomy was performed at completion of chemotherapy in 22 patients. Histological findings were no tumor in 13; mature teratoma in 5; immature teratoma in 1; active disease in 3. Six of the latter nine patients had persistent radiologic abnormalities after chemotherapy. All three patients with active disease had elevated serum tumor markers. Five out of the six patients with residual teratoma lesions had a teratoma component in the primary tumor. According to histological findings at second-look surgery, the number of patients without long-term evidence of disease is 12, 5, 1 and 0, respectively. Eighteen patients were not subjected to second-look surgery. One of them had clearly progressive disease and the other 17 experienced a clinical complete response at completion of chemotherapy. All patients but one are alive without evidence of disease. We conclude that second-look surgery is not necessary in patients with elevated serum tumor marker levels and in those patients with neither radiologic abnormality nor teratoma element in the primary tumor. However, we recommend a second-look procedure for the small subset of patients with a teratoma component in the primary tumor and persistent radiologic abnormalities along with normal serum tumor markers at the end of chemotherapy.

KEY WORDS: ovary, germ-cell tumors, surgery, second-look

INTRODUCTION

Malignant germ cell tumors of the ovary account for <5% of all ovarian neoplasms and occur mainly in girls and young women. The last two decades have seen great improvements in the diagnosis and management of patients with ovarian germinal neoplasms. The initial treatment approach is surgery, which both establishes diagnosis and initiates therapy. Subsequent cisplatin-based chemotherapy is required in the majority of cases [1]. With epithelial ovarian cancer as a template, second-look laparotomy (SLL) has been recommended by some

Accepted for publication January 10, 1996.

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investigators for the routine management of ovarian germ cell tumors [2–4]. However, others have questioned its use [5–7].

We report here our experience with postoperative primary chemotherapy in the management of ovarian germ cell tumors and focus on the role of second-look laparotomy according to the different histological subtypes.

MATERIALS AND METHODS

From September 1976 to December 1992, 40 patients with malignant germ cell neoplasms of the ovary received postoperative chemotherapy. All but six patients underwent initial surgery outside our institution. Histological materials were systematically reviewed by one of us (P.D.). The tumors were staged according to the International Federation of Gynecology and Obstetrics (FIGO) classification system.

Various cisplatin-based combinations were used: VAB-like regimens (actinomycin-D + cyclophosphamide + vinblastine or vincristine + bleomycin + cisplatin ± doxorubicin) in 15 patients [8]; BEP or EP regimens (etoposide + cisplatin ± bleomycin) in 12 patients [9]; PVeBV (double dose cisplatin + vinblastine + bleomycin + etoposide) in 9 patients [10]; and other regimens in 4 patients.

A radiologic evaluation was made at completion of chemotherapy with ultrasonography and/or computed tomography of the abdomen and pelvis. Before 1988, SLL was systematically performed at completion of chemotherapy. Afterwards, the procedure was required only in case of persistent radiologic abnormalities. The surgical procedure was done specifically to assess tumor pathology and extent and to resect residual disease. Any apparent residual mass was to be removed if possible, and if not, appropriate biopsies were taken. Washings and multiple biopsies of peritoneal surfaces (pelvis, paracolic gutters, and undersurfaces of the diaphragm) were performed. Normal serum tumor marker levels (human chorionic gonadotropin [hCG] and/or alphafetoprotein [AFP]) were not specifically required before second-look surgery.

After the end of therapy, patients were followed every 2 months during 1 year and at gradually increasing intervals thereafter. Survival was measured from the time of diagnosis to the time of death or until January 1, 1995, whichever came first.

TABLE I. Initial Characteristics of the Population

Characteristic		Patient number
Age (year)		
Mean	22	
Range	15–59	
Side		
Right		18
Left		15
Bilateral		6
Unknown		1
Histological type		
Pure tumors		
Dysgerminoma		6
Immature teratoma		9
Endodermal sinus tumor		11
Mixed tumors		
With teratoma component		9
Without teratoma component		5
Performance status		
0		27
1		11
2		2
FIGO stage		
IA		8
IB		2
IC		9
IIA		1
IIC		2
IIIA		2
IIIB		6
IIIC		7
IV		3
Primary surgery[a]		
UO		9
UO + O		4
USO		10
USO + TH		3
BSO		1
BSO + TH		3
BSO + TH + O		7
Biopsy alone		3
Residual disease		
None		25
<2 cm		7
>2 cm		8
Chemotherapy regimen		
VAB-like		15
PVeBV		9
BEP/EP		12
Others		4

[a]UO = unilateral oophorectomy; O = omentectomy; USO = unilateral salpingo-oophorectomy, BSO = bilateral salpingo-oophorectomy, TH = total hysterectomy. Protocol acronyms are detailed in the text

RESULTS

Forty patients with ovarian germ-cell tumors received postoperative first-line chemotherapy. Their initial characteristics are described in Table I. Twenty-two patients did not have elements of teratoma, having pure dysgerminoma (6 patients), pure endodermal sinus tumor (11 patients), or a mixed germ-cell tumor lacking teratoma (5 patients). Twenty-three patients underwent a primary conservative surgery. Three patients had only a biopsy before chemotherapy because of stage IV disease. A SLL was performed at completion of chemotherapy in 22 patients. The surgical findings are shown in Table II.

Twenty-five patients had no macroscopic residual disease after primary surgery. Twelve patients were subjected to SLL after adjuvant chemotherapy. All of them had normal serum tumor markers and no radiologic abnormal-

TABLE II. Histological Findings at Second-Look Surgery According to Tumor Histology and Residual Disease After Primary Surgery

Residual disease after primary surgery	Teratoma component in primary tumor	Surgical findings at second-look laparotomy			
		Negative	Mature teratoma	Immature teratoma	Active disease
No	No	4	1	0	0
	Yes	6	0	1	0
Yes	No	3	0	0	3
	Yes	0	4	0	0
Total		13	5	1	3

ity at completion of chemotherapy. Ten patients had no tumor at surgery. One patient with an initially stage IA pure endodermal sinus tumor was found to have small peritoneal implants of mature teratoma. Another patient had grade 1 immature teratoma lesions at SLL. The initial diagnosis was a stage IA grade 3 immature teratoma. SLL allowed the complete excision of teratoma lesions in these two patients. All 12 patients received no further chemotherapy. They remain free of disease 24–192 months after diagnosis.

Thirteen patients without macroscopic residual disease after primary surgery did not undergo SLL. One patient with a stage IC grade 2 immature teratoma had a progressive disease while on first-line chemotherapy but was subsequently rendered free of disease with a salvage chemotherapy including etoposide, ifosfamide, and cisplatin (VIP regimen). The other 12 patients had no radiological abnormality at completion of chemotherapy. Eleven patients remain free of disease without any further therapy 40–204 months after diagnosis. Only one patient experience a huge peritoneal relapse 6 months after completion of first-line treatment. She had initially a stage IC endodermal sinus tumor and rapidly died of progressive disease 14 months after diagnosis.

Fifteen patients received chemotherapy for residual disease after primary surgery. Ten patients were subjected to SLL. Three patients with normal serum tumor markers and no radiologic abnormality at completion of chemotherapy had no tumor at surgery. However, one of them, who initially had a stage IV endodermal sinus tumor, rapidly relapsed and died of disease 18 months after diagnosis. The other two patients remain free of disease 48 and 168 months after diagnosis. Seven patients had persistent radiologic abnormalities after chemotherapy. Three of them had a clearly progressive disease with increasing serum tumor markers. The second-look procedure revealed aggressive histologies. All three patients died of progressive disease 12, 13, and 24 months after diagnosis. The other four patients had normal tumor markers at time of surgery. Mature teratoma lesions were removed in all patients. Primary tumor histologies were pure immature teratoma in three patients and a mixed germ-cell tumor including teratoma elements in one patient. All four patients are free of disease 48–76 months after diagnosis. However, one of them experienced a subsequent peritoneal relapse 64 months after diagnosis. A third laparotomy allowed the complete excision of mature teratoma lesions.

TABLE III. Results of Radiologic Evaluation at Completion of Chemotherapy and Histological Findings at Second-Look Surgery

Persistent radiologic abnormalities	Surgical findings at second-look laparotomy			
	Negative	Mature teratoma	Immature teratoma	Active disease
Yes	0	4	0	3
No	13	1	1	0
Total	13	5	1	3

Five patients with residual disease after primary surgery did not undergo SLL after first-line chemotherapy. All of them achieved a complete clinical and biological response. One patient with a pure endodermal sinus tumor relapsed after 17 months with liver metastases and died despite a salvage chemotherapy with the VIP regimen. Another patient with an initial mixed germ-cell tumor experienced a contralateral ovarian relapse with lung metastases. She is free of disease 26 months after the end of the salvage chemotherapy with the VIP regimen. The other three patients are alive without evidence of disease 48–98 months after diagnosis.

The relationship between the radiologic evaluation at the end of chemotherapy and histological findings at SLL is shown in Table III. When persistent radiologic abnormalities were detected, the second-look surgery systematically revealed germ-cell tissues, including mature teratoma in four patients and active disease in three cases. Conversely, the SLL allowed the excision of mature teratoma lesions in two out of 15 patients without radiologic abnormality. One of these two patients had a mature teratoma component in the primary tumor.

The long-term results of the 40 patients are summarized in Table IV. Eighteen of the 22 patients who underwent SLL are free of disease. One lethal relapse was observed

TABLE IV. Outcome of Patients According to Disease Status at End of First-Line Treatment

	Number of patients	
	At the end of first-line treatment	Without evidence of disease
Second-look surgery	22	18
■ Negative	13	12
■ Teratoma	6	6
■ Active disease	3	0
No second-look surgery	18	17
■ Clinical complete response	17	16
■ Progressive disease	1	1

among patients with negative histological findings. All four patients with active disease died. Seventeen of the 18 patients who were not subjected to SLL are alive without evidence of disease. Overall, 35 out of 40 patients are alive without evidence of disease 24–204 months after initial diagnosis.

DISCUSSION

Our data clearly support the impact of cisplatin-based chemotherapy in the postoperative management of malignant ovarian germ cell tumors. The overall survival of 87.5% with a median follow-up of 8 years is satisfactory. It is noteworthy that all failures were observed in patients with nondysgerminomatous tumors.

Until the advent of combination chemotherapy in the mid-1960s, the prognosis of patients with nondysgerminomatous tumors of the ovary was dismal. All patients with advanced disease died. Only 5–20% of patients with stage I disease survived after treatment with surgery alone or single-agent chemotherapy [11–13]. The first effective progress was reported with a combination of vinblastine, actinomycin-D, and cyclophosphamide (VAC regimen). Two decades of experience with VAC revealed a high proportion of cure in stage I disease (85%). However, the sustained remission rate was <50% in patients with advanced disease [14]. Subsequently, the successful introduction of cisplatin into clinical trials for male germ cell cancer prompted investigators to use cisplatin-based regimens in patients with ovarian germinal neoplasms. In the largest study performed by the Gynecologic Oncology Group (GOG) with a combination of cisplatin, vinblastine, and bleomycin (PVB), 89 patients with advanced or recurrent tumors were evaluated. Forty-seven (53%) patients were free from progression at 2 years with a median follow-up of 4 years [15]. In a recently published trial of the GOG, 93 patients with stages I–III completely resected tumors were treated with three postoperative cycles of BEP. Ninety-one patients were clinically free of recurrent germ cell tumor with a median follow-up of 3 years [16].

Promising results were also reported in metastatic disease, but more extensive investigations are required to draw a firm conclusion [9]. Alternative regimens without etoposide [8] or including double doses of cisplatin [10] do not appear to increase the efficacy. These data favor etoposide and cisplatin based regimens as standard chemotherapy in the 1990s.

The development of chemotherapy in ovarian dysgerminomatous tumors was prompted by other reasons. Dysgerminoma is radiosensitive, and several studies documented a radiocurability of 60–100% in the postoperative treatment of patients as well as in recurrent disease [17,18]. However, abdominopelvic radiotherapy, even with the rather low doses used in dysgerminoma, is associated with ovarian failure and sterility [19]. So chemotherapy has been developed as an alternative treatment that could produce equivalent results while preserving the reproductive capacities [20]. In a report of the GOG experience, 20 patients with incompletely resected disease were treated with either PVB or BEP regimens. Fourteen second-look procedures were performed and demonstrated pathological complete responses in all patients. Overall, 19 of the 20 patients remained free of disease with a median follow-up of 26 months [21].

The high efficacy of chemotherapy in ovarian germ cell tumors may question the role of second-look laparotomy. In epithelial ovarian cancer, the inherent inaccuracy of clinical staging has led to the use of reassessment laparotomy. However, the impact of histological findings at second-look laparotomy on patient management and outcome is unclear. Yet, in testicular germ tumors, post-chemotherapy surgery is an important component of the treatment [22]. In particular, some patients may benefit from resection of persistent teratoma [23]. Indeed, teratoma may grow and cause multiple organ damage [24] or undergo subsequent malignant transformation [25]. In germ-cell tumors of the ovary, some authors have recommended second-look laparotomy. The arguments supporting this statement were the possible impact on cure with further therapy [2–4]. The largest experience in the literature with second-look surgery was recently published by the GOG [7]. In reporting 117 patients who were subjected to this procedure between 1979 and 1991, Williams et al. [21] suggested that second-look laparotomy was not

necessary in patients with no residual disease after primary surgery or in these patients with advanced tumors that do not contain teratoma component. Only the subgroup of patients with incompletely resected tumors containing teratoma elements appeared to have a substantial likelihood of benefitting from second-look surgery [7]. Similarly, in the series reported by Gershenson et al. [6] none of the 53 patients undergoing second-look laparotomy had their management course modified as a result of that surgery. It is noteworthy that no radiologic investigation was performed at completion of chemotherapy in these studies.

The present report clearly confirms that the role of second-look surgery is limited to a small subset of patients. Among 23 patients who underwent a reassessment laparotomy after chemotherapy, only six who had complete resection of mature or immature teratoma did benefit from this procedure. Conversely, neither the 13 patients with negative findings, 12 of whom are free of disease, nor the four patients with active diseases who subsequently died of progressive disease derived any benefit from surgery. It is noteworthy that five of the six patients with teratoma lesions at second-look reassessment had a teratoma component in the primary tumor and persistent radiologic abnormalities after chemotherapy. Among 21 patients who did not undergo second-look surgery, only two patients who experienced subsequent relapse could have benefitted from such a procedure if residual disease had been found. However, the efficacy of salvage therapy is rather moderate. These results also suggest a better efficacy of radiologic investigations in assessing residual disease as compared to epithelial tumors. A systematic radiologic assessment including ultrasonography and/or computed tomography should be performed at completion of chemotherapy with the aim of refining the indication of SLL.

The role of chemotherapy after excision of immature teratoma grade 1 lesions remains questionable [7]. There is little information about the pathology and biology of postchemotherapy ovarian teratomas. In testicular germ-cell tumors, this histological finding does not require any further therapy, unless nongerm-cell elements are seen [23]. In the GOG experience, all four patients with immature teratoma grade 1 lesions, three of whom received postoperative VAC, remain free of disease [7]. In the present study, one patient refused any further therapy after second-look surgery. She is alive without evidence of disease 60 months after the end of treatment.

We conclude that second-look surgery is mandatory only in the patients with a teratoma component in the primary tumor and persistent radiologic abnormalities along with normal serum tumor markers at the completion of chemotherapy.

ACKNOWLEDGMENTS

The authors thank C. Molinazzi for excellent secretarial assistance during preparation of the manuscript.

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